Synthesis of Carbon-14 Labeled Isocyanates. Determination of the Carbon-14 Distribution in the Isocyanate Groups of 2,4-Tolylene Diisocyanate[1]

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ABSTRACT

A practical phosgenation procedure has been devised for the preparation of isocyanates labeled with C^{14}. Three such isocyanates: 2-tolyl isocyanate, 4-tolyl isocyanate, and 2,4-tolylene diisocyanate (TDI) were prepared. The C^{14} distribution in the latter was determined by scintillation counting of some of its derivatives, one of which was 3-amino-4,2',6'-trimethylcarbanilide, from which the fraction of C^{14} in the 4-isocyanate group of TDI was obtained.

Introduction

Poly(urethanes) prepared from poly(propylene oxide) and 2,4-tolylene diisocyanate (I) labeled with C^{14} in the isocyanate groups have been used in the study of polymer degradation mechanisms.[2] Because of the high sensitivity of radioactivity measurements, very small extents of bond scission can be detected, and specific reactions can easily be followed during the course of the degradative process. The labeled diisocyanate (I) can be readily prepared

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[1]This paper represents one phase of research performed by the Jet Propulsion Laboratory, California Institute of Technology, sponsored by the National Aeronautics and Space Administration, contract NAS7-100.

[2]Simha, R., J. D. Ingham, N. S. Rapp and J. P. Hardy, J. Polymer Sci., B 2 675-679 (1964).

from 2,4-tolylene diamine or its dihydrochloride and C^{14} enriched phosgene. However, the distribution of C^{14} in the 2- and 4- positions depends upon the kinetics and mechanism of diisocyanate formation including accompanying isotope effects. It also depends to a large extent on the particular set of experimental conditions employed for the preparation. Procedures for the syntheses of labeled 2,4-tolylene diisocyanate, 2-tolyl isocyanate, and 4-tolyl isocyanate in a closed reaction system are described in this paper, as well as the method by which the C^{14} distribution in the diisocyanate was determined.

Results and Discussion

The diisocyanate (I) can be prepared by direct phosgenation of the corresponding diamine or diamine dihydrochloride.[3,4] In this work the dihydrochloride was used in order to suppress undesired side reactions more effectively. Ordinarily, phosgene can be bubbled directly into the reaction mixture; however, because of the probable loss of excess phosgene, this is relatively impractical when C^{14}-phosgene is employed. Therefore, the reaction was conducted in a closed system at moderate pressure. This modification can be applied to the preparation of a large number of isocyanates or diisocyanates by phosgenation.

The C^{14} distribution in (I) was established by performing a sequence of reactions in which the carbon atom of one of the isocyanate groups was removed exclusively, followed by specific radioactivity determinations of the product (III) and also of the derivatives (IV) and (V). The appropriate reactions included:

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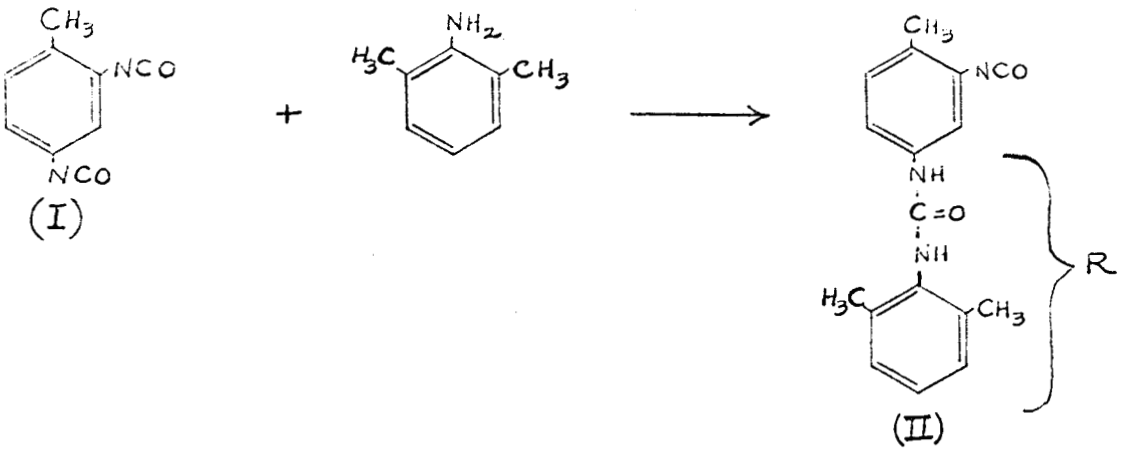
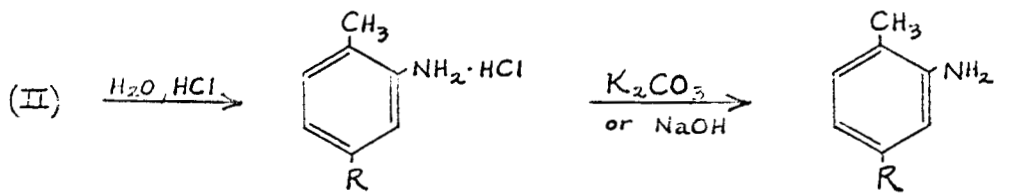
[3] Siefken, W., Ann., 562, 75-136 (1949).

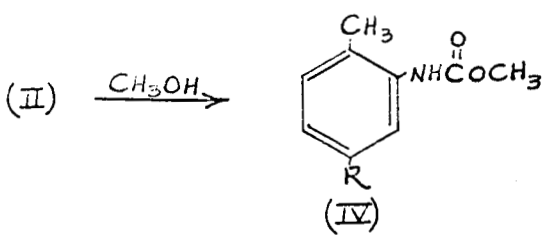
[4] Hart, W. F., M. E. McGreal and P. E. Thurston, J. Org. Chem., 27, 338-340 (1962).



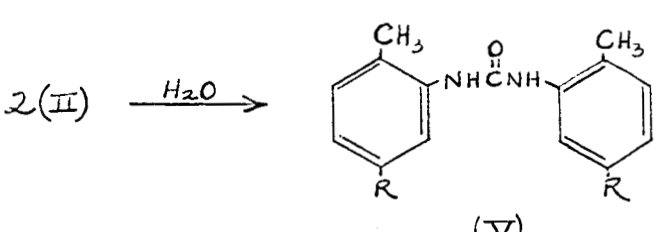
(I) (II) (A)



(III) (B)



(IV) (C)



(V) (D)

Previous work had shown that the reaction of equimolar amounts of aniline and (I) followed by acidic hydrolysis of the product and subsequent neutralization gave a 68% yield of 3-amino-4-methylcarbanilide.[5] In the present work 2,6-dimethylaniline was used to increase the probability of exclusive reaction of the amine at the isocyanate group in the 4-position. The yield of (II) was 87%, m.p. 207-209°C. Conditions for the reactions shown by equations (B), (C), and (D) were also established, and the amine (III), urethane (IV), and urea (V) were obtained in yields of 96, 96, and 97% respectively. Reaction (C) was carried out so that the specific activity of (I) could be determined from the less reactive urethane derivative since it had been found that isocyanates gave erratic results when counted directly in the scintillation spectrometer.

Thin-layer chromatography was used to ascertain the purity of the amine (III) and urethane (IV), and hence, by inference, the purity of (II). The urea (V) was much too insoluble a substance to yield to chromatographic investigation. Three chromatograms of the two substances were run in three different developing solvent systems. The results are summarized in Table I. It can be seen that both (III) and (IV) gave only one strong spot and a second much less intense spot. These results confirmed that a relatively high degree of purity existed in the samples of (III) and (IV) which were prepared.

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[5] Simons, D. M. and R. G. Arnold, J. Am. Chem. Soc., 78, 1658-1659 (1956)

Table I.

Results of TLC Studies of (III) and (IV)

Solvent System	R_f Values and Relative Spot Intensities	
	(III)	(IV)
Benzene/pyridine (4:1)	0.46: strong 0.525: faint	0.525: strong 0.575: faint
Chloroform/methanol (9:1)	0.54: faint 0.595: strong	0.825: faint 0.875: strong
Ethyl acetate/cyclohexane (9:1)	0.55: faint 0.68: strong	- - - 0.825: strong

Although very good elemental analyses were obtained for (I), (II), (IV), and (V), it was difficult to obtain a good elemental analysis for (III). As a result, proton nuclear magnetic resonance (n.m.r.) was used to obtain further evidence of its structure. Initially a spectrum in deuterated chloroform solution was obtained; however, the solubility in chloroform was $\sim 0.5\%$ and the amino proton signal was not observed. Probably exchange of the amino hydrogens of (III) with deuterium from the solvent suppressed the amino proton resonance. Although the solubility was only $\sim 3\%$ in pyridine and the aromatic protons were obscured

by solvent resonances, pyridine solutions gave satisfactory spectra as shown in Figure 1. The resonance signals at 4.98, 2.29 (side band at 2.35 ppm), and 2.11 ppm (side band at 2.04 ppm) are assigned to the amino, 2',6'-dimethyl, and 4-methyl protons, respectively. Electronic integration gave an average of 2.0:6.2:8.0 for the ratio of amino:2',6'-dimethyl:4,2',6'-trimethyl protons compared with a theoretical ratio of 2:6:9. Planimeter integration gave less satisfactory agreement, 2.0:4.5:6.9. However, it is believed that the planimeter integrations are more accurate, and that the amino proton signal is increased by exchange with adventitious water. The reason for placing more confidence in the planimeter integrations is based on the value obtained for the 2',6'-dimethyl: 4-methyl proton ratio as determined by the two different integration methods. This ratio cannot be anything but 2:1, and electronic integration gave an average value of 3.5:1.0. The same integration performed with a planimeter gave the ratio 1.9:1.0. Recalculating the planimeter figures, the following ratios were obtained: amino:2',6'-dimethyl protons = 2.7:6.0; amino:4,2',6'-trimethyl protons = 2.6:9.0. The corresponding calculated values are 2:6 and 2:9, respectively.

A curious phenomenon occurred after the same pyridine solution of (III) which gave the spectrum pictured in Fig. 1 was filtered in order to remove a very small amount of undissolved solid which was suspended in it. A spectrum of the filtered solution (Fig. 2) revealed that the amino proton resonance signal had increased and was greater even than that of the 2',6'-dimethyl protons. In addition, the chemical shifts of the various peaks had changed somewhat to 4.90 ppm for the amine protons and 2.32(side band at 2.38 ppm)

and 2.14 ppm (side band at 2.08 ppm) for the dimethyl and methyl protons. Upon integrating, the values of the ratios of the areas under the various peaks obtained by electronic integration corresponded much more closely in this case to those obtained with a planimeter. The former gave the following figures: 2',6'-dimethyl:4-methyl protons = 1.9:1.0; amino:2',6'-dimethyl protons = 7.3:6.0; amino:4,2',6'-trimethyl protons = 7.2:9.0. The same ratios obtained by planimeter integration were 2.0:1.0, 7.8:6.0, and 7.8:9.0 respectively. The explanation which is offered for the increased size of the amine peak is that additional water must have been picked up by the solution during filtration, since adding a drop of water to a pyridine solution of (III) produced the same effect.

The origin of the side bands which accompany both of the methyl peaks in the spectra of pyridine solutions of (III) is not known with certainty. When a spectrum in pyridine was taken at elevated temperatures (80° and 100° C), the intensity of the side bands was significantly decreased. Further investigation also showed that a 3% solution of (III) in the binary solvent system 88% phenol/12% water gave a spectrum in which the methyl peaks are completely devoid of any side bands (Fig. 3). The chemical shifts of the 2',6'-dimethyl and 4-methyl peaks in this spectrum are 2.12 and 1.83 ppm respectively, and the ratio of their average areas as determined by planimeter integration is 2.1:1.0. The spectrum of a solution of (III) in 2,2,2-trifluoroethanol also did not show any side bands associated with the methyl peaks. All of these facts seem to indicate the possibility that complex formation is occurring in the solvent pyridine at room temperature.

One other step was taken to establish the identity of the product obtained from reaction (B), and that was to hydrolyze a sample of the isocyanate (II) in dilute sodium hydroxide solution. The only product expected from this basic hydrolysis was 3-amino-4,2',6'-trimethylcarbanilide (III). Comparison of the infrared spectra of the basic hydrolysis product and the one obtained from reaction (B) showed the two to be identical. The consistency found in the radioactivity data which will follow is also indicative of the reasonableness of the assignment of the amine (III) as the product of reaction (B).

The specific activities of the amine (A_{III}), urethane (A_{IV}), and urea (A_V) were determined in two separate scintillation counting experiments. Because of the insolubility in the scintillator solution of the materials to be counted, the suspension counting technique was employed using Cab-O-Sil as the suspending agent. Since the specific activity of the urethane (A_{IV}) is equal to that of the diisocyanate (A_I) and the specific activity of the amine (A_{III}) represents the contribution of only the 4-isocyanate group to A_I, then the fraction of C^{14} at the 4-position of (I) can be calculated from

$$F_p = A_{III} / A_{IV} \qquad (1)$$

Two other expressions for F_p can easily be derived which involve the specific activity of the urea (A_V). In one of these equations, A_V is used in conjunction with A_{III} to give:

$$F_p = \frac{A_{III}}{A_V - A_{III}} \qquad (2)$$

Using A_V and A_{IV}, it can also be shown that

$$F_p = \frac{A_V - A_{IV}}{A_{IV}} \qquad (3)$$

Substituting the experimental data obtained into these three expressions, values of F_p were calculated and are given in Table II.

Table II.

Calculated Values of F_p, the Fraction of C^{14} in (I) Located at the 4-position

Equation	F_p, Exp. 1[a]	F_p, Exp. 2[b]
(1)	0.646	0.656
(2)	0.621	0.749
(3)	0.688	0.532
(Ave)	0.652	0.646

[a] $A_{III} = 5.96 \times 10^8$, $A_{IV} = 9.22 \times 10^8$, and $A_V = 15.56 \times 10^8$ dpm/mole

[b] $A_{III} = 6.13 \times 10^8$, $A_{IV} = 9.34 \times 10^8$, and $A_V = 14.31 \times 10^8$ dpm/mole

The results plainly show a higher concentration of C^{14} at the 4-position (~ 65%) than at the 2-position. Such a distribution is indeed reasonable when one considers the manner in which the labeled 2,4-tolylene diisocyanate was prepared. In the first place, the starting material was the dihydrochloride of 2,4-tolylene diamine. Thus, it was necessary for free amine to be generated before any reaction at all could occur with phosgene. Based on the literature values of K_b for o- and p-toluidine which show the latter to be a considerably stronger base, one would expect a much faster conversion rate to the free amine at the 2-position of 2,4-tolylene diamine dihydrochloride and hence a greater abundance of the reactive species at this site. Combined with the fact that initially only unlabeled phosgene was present in the reaction mixture, much more of the 2-isocyanate group was likely already formed before the labeled phosgene was even introduced. Thus, reaction of an amino group with phosgene containing C^{14} was enhanced at the 4-position simply by the larger number of sites available there for reaction after the labeled gas was admitted to the system. By altering the time differential between the introduction of unlabeled and labeled reactant, it is expected that the distribution of C^{14} in 2,4-tolylene diisocyanate can be varied over a wide range.

Experimental

Preparation of Labeled 2,4-Tolylene Diisocyanate (I).

Freshly distilled 2,4-tolylene diamine (3.3 g) was dissolved in 125 ml of dry toluene in an aerosol bottle. Dry hydrogen chloride was bubbled into the solution to form the amine dihydrochloride. After placing a sealed ampule of

labeled phosgene (0.5 mC) into the bottle, it was fitted with a pressure gauge and gas inlet valve. Unlabeled phosgene (~ 5.5 g) was then let into the bottle, and after closing the inlet valve, the sealed tube of labeled phosgene was broken by vigorously shaking the reactor. This mixture was heated behind a shield in a hood until a pressure of ~ 110 psi was obtained. After 2 hrs. the bottle was cooled, and then opened and evacuated through a large charcoal trap (to collect unreacted hydrogen chloride, phosgene, and most of the toluene). After filtration of the reaction mixture, the remaining solvent was removed, and the crude diisocyanate was distilled under reduced pressure using unlabeled TDI as a diluent and chaser. The radioactive yield was 41%.

Anal. Calcd. for $C_9H_6O_2N_2$: C, 62.07; H, 3.45; N, 16.09.

Found: C, 62.24; H, 3.40; N, 15.91.

The refractive index, n_D, was 1.5662 at 23°C compared with a literature value[6] of 1.5654 at 25°C. The dimethyl urethane derivative was also prepared, m.p. 171-171.5°C, and it gave a mixed m.p. with an authentic sample of 170-171°C.

Preparation of Labeled 2-Tolyl and 4-Tolyl Isocyanate.

Two tolyl isocyanates were prepared from the corresponding toluidine hydrochlorides by essentially the same procedure as above, except that benzene was used as the solvent and labeled phosgene was released prior to admission of unlabeled phosgene to the system. 2-Tolyl isocyanate was obtained in 62% radioactive yield.

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[6] Saunders, J. H. and K. C. Frisch, "Polyurethanes: Chemistry and Technology, Part I. Chemistry," Interscience, New York, N.Y., 1962, p. 348.

Anal. Calcd. for C_8H_7ON: C, 72.18; H, 5.26; N, 10.53.

Found: C, 72.16; H, 5.28; N, 10.32.

$n_D^{23.4} = 1.5336$ compared with $n_D^{24} = 1.5338$ for an authentic sample.

4-Tolyl isocyanate was obtained in 74.5% radioactive yield.

Anal. Calcd. for C_8H_7ON: C, 72.18; H, 5.26; N, 10.53.

Found: C, 72.29; H, 5.42; N, 10.36.

$n_D^{24} = 1.5292$ compared with $n_D^{24} = 1.5298$ for an authentic sample.

4,2',6'-Trimethyl-3-isocyanatocarbanilide (II).

2,6-Dimethylaniline was dried over potassium hydroxide and then vacuum distilled with a dry nitrogen capillary leak three times from zinc dust. The colorless, freshly distilled amine (2.54 g, 0.0210 mole) was weighed out in a dry box and dissolved in 50 ml of anhydrous tetrahydrofuran (distilled from lithium aluminum hydride). C^{14} - Labeled TDI (3.00 ml, 3.66 g, 0.0210 mole) was dissolved in 100 ml of the same solvent. The separatory funnel containing the amine solution was connected to the flask which contained the TDI solution. After removing the assembled apparatus from the dry box, the TDI solution was first cooled in an ice-salt water bath, and then the aniline solution was added dropwise with constant stirring. The time of addition was 30 minutes during which the bath temperature was maintained between -5° and -10°C. About 5 minutes after completion of the addition, the white adduct began to precipitate. After a total reaction time of 18 hours, the solid was removed by filtration and washed thoroughly with hexane. After drying, the product was found to weigh 5.37 g for a yield of 86.6%. It melted at 207-209°C.

Anal. Calcd. for $C_{17}H_{17}O_2N_3$: C, 69.14; H, 5.80; N, 14.23.

Found: C, 69.18; H, 5.88; N, 14.20.

Acidic Hydrolysis of (II).

The isocyanate (II) (0.3056 g) was stirred for 30 minutes in 100 ml of anhydrous tetrahydrofuran. After removing 0.0616 g that did not dissolve, 50 ml of 6 N hydrochloric acid was added dropwise with constant stirring over a period of one hour. The maximum temperature reached during this time was 39°C. The reaction mixture was stirred for an additional hour, and then it was neutralized with a concentrated solution of sodium hydroxide. The temperature during neutralization did not exceed 56°C. The salted out tetrahydrofuran layer was separated, and the solvent was removed under reduced pressure. The solid product was washed with water and dried. The yield of product, believed to be the amine (III), was 0.2132 g or 95.8%. Its m.p. exceeded 300°C, but degradation was believed to have occurred below this temperature since the compound gradually turned brown as the temperature of the melting point block was increasing. The elemental analyses were not in very good agreement with the calculated values:

Anal. Calcd. for $C_{16}H_{19}ON_3$: C, 71.35; H, 7.11; N, 15.60.

Found: C, 68.20; H, 6.58; N, 14.79.

The ratio of the percentages of C, H, and N found, however, is very close to the calculated ratio, suggesting the possibility of salt contamination.

Methanolysis of (II).

The isocyanate (II) (0.5907 g, 0.002 mole) was placed in 25 ml of anhydrous methanol, and the suspension was heated to reflux with stirring. After 15 minutes a small amount of solid (0.0106 g) remained undissolved, and

it was removed from the reaction mixture by filtration. Methanol was then removed from the filtrate under reduced pressure to give a white solid which was collected and washed with hexane. The yield of product (IV) was 0.6195 g or 96.3%, and it melted at 214-219°C.

Anal. Calcd. for $C_{18}H_{21}O_3N_3$: C, 66.04; H, 6.47; N, 12.84.

Found: C, 66.13; H, 6.53; N, 12.85.

Neutral Hydrolysis of (II).

The isocyanate (II) (0.5907 g, 0.002 mole) was weighed into a 50 ml flask and suspended in 20 ml of distilled water with 5 ml of tetrahydrofuran added as a wetting agent. This mixture was refluxed for five hours, and then the product was removed by filtration and dried. The white solid weighed 0.5504 g, making the yield of urea (V) 97.5%. This compound neither melted nor showed any signs of decomposition under 300°C.

Anal. Calcd. for $C_{33}H_{36}O_3N_6$: C, 70.19; H, 6.43; N, 14.88.

Found: C, 70.12; H, 6.50; N, 14.68.

Thin-layer Chromatography of (III) and (IV).

Silica Gel G (30 g) was uniformly mixed with 60 ml of distilled water, and the resulting suspension was transferred to a Desaga spreader with the layer thickness regulator set at 250 μ. Five 20 X 20 cm glass plates were coated with this slurry. After coating, the adsorbents were activated by heating the plates overnight at 100°C. Solutions of the amine (III) and urethane (IV) were prepared in volumetric flasks by dissolving 2.0 mg in 2.00 ml of chloroform. Ten microliters of each solution was applied to three of the plates with a

microsyringe. The chromatograms were then run in three different developing solvent systems. These consisted of: 120 ml of benzene and 30 ml of pyridine; 135 ml of chloroform and 15 ml of methanol; and 135 ml of ethyl acetate and 15 ml of cyclohexane. The plates were removed from the developing tanks after the solvent front had advanced 100 mm from the origin. They were first air dried and then heated ~ 72 hrs. in an oven at 100°C. The spots could be observed most clearly under long wave ultraviolet light. In all cases but one, two spots were observed, one of which was always much more intense than the other. The various R_f values are given in Table I.

Nuclear Magnetic Resonance Spectra of (III).

The n.m.r. spectra were obtained with a Varian A-60 Spectrometer. Because of the insolubility of the amine (III) in deuterated chloroform, the most useful spectra were obtained in pyridine or a solvent mixture consisting of 88% phenol/12% water at a concentration in either solvent of ~ 3%.

Determination of Radioactivity by Scintillation Spectrometry.

Carbon-14 in (III), (IV), and (V) was counted with a Packard Tri-Carb Liquid Scintillation Spectrometer. The scintillator solution was toluene containing PPO (2,5-diphenyloxazole, 5 g/l) and dimethyl POPOP (1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene, 0.3 g/l) as the primary and secondary scintillators respectively. The samples prepared for counting contained 0.1 mmole in the case of (III) and (IV) and 0.05 mmole of (V), 0.87 (Exp. 1) or 1.10 g (Exp. 2) of Cab-O-Sil, and 15.00 ml of the scintillator solution. Each sample was counted for a total of approximately 500 minutes. The

instrumental efficiencies for the two experiments were ~60 and 58.5% respectively. Carbon-14 labeled toluene (specific activity = 4.38×10^4 disintegrations/min/ml) was used as the internal standard. Solvent efficiencies in Exp. 1, were ~16, 64, and 55% for (III), (IV), and (V); in Exp. 2 the corresponding efficiencies were ~28, 94, and 82.5%. The increased efficiency was undoubtedly due to the use of a freshly prepared scintillator solution in Exp. 2. The blanks from the two experiments had solvent efficiencies of ~60 and 83%. Thus, only the amine (III) produced significant quenching.

Figure Titles

1. The proton n.m.r. spectrum of the amine (III) in pyridine at 60 megacycles.

2. The proton n.m.r. spectrum of the amine (III) in pyridine at 60 megacycles after filtration.

3. The proton n.m.r. spectrum of the amine (III) in phenol-water solution at 60 megacycles.